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New assessment of platelet deposition in small caliber vascular prostheses using technetium-99m apcitide scintigraphy in rabbit model

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INTRODUCTION

A high antithrombogenicity is one of essential factors for the successful development of small caliber vascular prostheses in peripheral or coronary artery bypass surgery. There is therefore a demand for methodology that can accurately evaluate platelet deposition in prosthetic vascular grafts.

The platelet deposition is traditionally assessed with Indium-111 (^{111}In) platelet scintigraphy([1-3]). This methodology is considered to be a useful technique to detect platelet deposition of the luminal surface of vascular grafts. Thakur ([4]) conjectured that ^{111}In-platelet scintigraphy has a good sensitivity and specificity for the investigation of platelet deposition because ^{111}In-platelets are incorporated directly into a growing thrombus. However, we recently reported the efficacy and limitation of ^{111}In-platelet scintigraphy in the assessment of platelet deposition in vascular prostheses ([5]). This technique has several drawbacks including a harvesting of autologous platelets, a long radiopharmaceutical half-life and a limited sensitivity.

Technetium-99m (^{99m}Tc) apcitide is a diagnostic radiopharmaceutical based upon a synthetic peptide that preferentially binds to glycoprotein IIb/IIIa receptors found on activated platelets. Although ^{99m}Tc-apcitide scintigraphy has been recently used for the detection of acute deep venous thrombosis([6-8]), there has been no report of its application to the assessment of platelet deposition in vascular prostheses. The purpose of this study was to investigate the efficacy of ^{99m}Tc-apcitide scintigraphy in the assessment of platelet deposition in small caliber vascular prostheses, compared with ^{111}In-platelet scintigraphy.

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Competition of interest: none.

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MATERIALS AND METHODS

Animal model

Thirty-six Japanese white rabbits weighting 2.5 to 3.5 kg were used for this study and divided into two groups by the selection of platelet scintigraphy: ^{99m}Tc-apcitide scintigraphy (Group I, 18 animals) or ^{111}In-platelet scintigraphy (Group II, 18 animals). The handling of laboratory animals and their use in experiments conformed to the "Guidelines for Animal Experiment at Kobe University Graduate School of Medicine" and "Guide for the Care and Use of Laboratory Animals" published by the National Academy Press([9]).

Surgical procedure

Animals were anesthetized with an initial intravenous dose of 20 mg/kg of pentobarbital sodium. Supplemental doses were given when required. Additional local anesthesia, containing 1% lidocaine, was applied in the cervical portion. Using sterile technique, a midline cervical incision was made and bilateral common carotid arteries were exposed. Following systemic heparinization (100 IU/kg), the grafts of 2cm length were interposed bilaterally in each animal. Anastomoses were performed in an end-to-end fashion with 8 to 10 stitches of interrupted sutures of 8-0 polypropylene. The common carotid arteries were declamped and patency of all grafts was evaluated by direct visualization before layered surgical closure. Neither antiplatelet nor anticoagulant therapy was administered after graft implantation. Totally, thirty-six grafts were implanted and evaluated in each group.

Vascular prosthesis

Experimental 2-mm internal diameter grafts were fibrin-coated knitted polyester vascular prostheses with an elastic spinal outer reinforce. The grafts were coated with fibrin glue as previously described([10]). Briefly, 20mL of blood from normal human donors was collected with 4mL of acid-citrate-dextrose (ACD) anticoagulant solution. Plasma was extracted by centrifugation

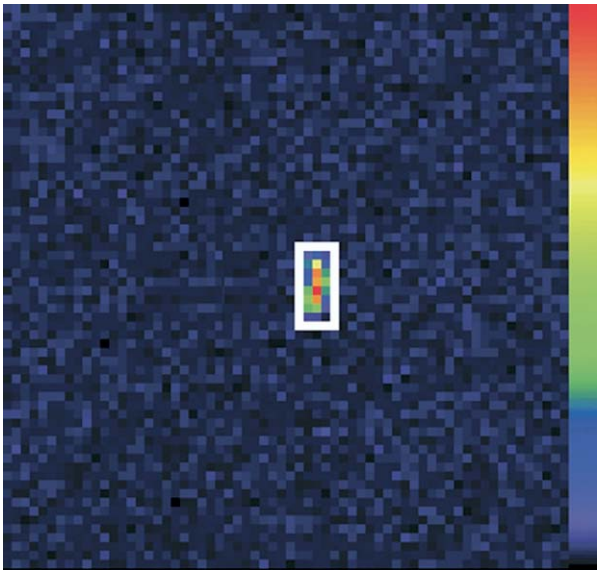

Fig 1. Graft region of interest (ROI) in semi-quantitative analysis. By using the iSSPView image program, graft ROI (10 x 5 pixels) was traced on the scintigraphic image of vascular prosthesis and the platelet activity of the graft ROI was measured.

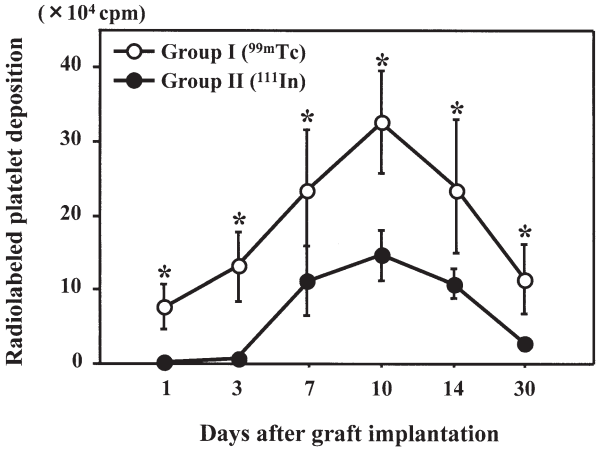

Fig 2. Radiolabeled platelet deposition of graft in quantitative analysis. Although there was no statistically significant difference in time-dependent changes of radiolabeled platelet deposition between both groups, the radiolabeled platelet deposition in Group I was significantly higher than that in Group II on each day after graft implantation. *P<0.001 vs. Group II.

at 1000G for 10 minutes at 4°C and filtered through a 0.22 μm filter for sterilization. After soaking the prosthetic graft in a solution containing 5000U of thrombin (Mochida Pharmaceutical Co., Tokyo, Japan) and 10% calcium chloride, the graft was clamped at one end and plasma was injected under pressure with a syringe until all pores were filled. Finally, the prosthesis was rinsed with heparinized Hank's buffer and air-dried at 25°C.

^{99m}Tc-apcitide scintigraphy

The ^{99m}Tc-apcitide was prepared from single-dose, sterile, non-pyrogenic lyophilized kits (AcuTect; Berlex Laboratories, Inc, Wayne, NJ) in accordance with the package insert. Briefly, each kit was formulated to contain 100μg of the peptide bibapcitide. To radiolabel the peptide with ^{99m}Tc, each kit was reconstituted with 1 to 3 mL of sterile, nonpyrogenic, oxidant-free sodium ^{99m}Tc-pertechnetate in 0.9% sodium chloride. The reconstituted kit was heated in a boiling water bath for 15 minutes and then allowed to cool before proceeding. At 1 hour before graft explantation, animals were injected with a dose of approximately 100 μg of the peptide bibapcitide radiolabeled with 740 MBq of ^{99m}Tc intravenously.

^{111}In-platelet scintigraphy

Autologous platelets were labeled with radioactive ^{111}In-oxine as previously described([4]). Briefly, 40mL of autologous blood was collected with 6mL of ACD anticoagulant solution through a catheter inserted in the ear artery of awaken rabbits, followed by isolation of platelet rich plasma by centrifugation (200G for 10 minutes). Platelets were pelletized by centrifugation (1000G for 10 minutes) and suspended in normal saline/ACD solution. Then platelets were incubated with 10 to 37 MBq of ^{111}In-oxyquinoline solution (Amersham international plc., UK) for 10 minutes at 37°C. After centrifugation (1000G for 10 minutes), the pellet was resuspended in 5mL of normal saline/ACD solution and reinjected intravenously at 24 hours before graft explantation.

Graft explantation

The grafts were explanted at 1, 3, 7, 10, 14 and 30 days after implantation (six grafts at each end point in each group) under the same general anesthesia as that of graft implantation. In graft explantation, patency of the grafts was determined by palpation of pulses in the graft and distal artery and heparin sodium (200IU/kg) was administrated intravenously to prevent blood clotting. Explanted grafts were immediately immersed and gently flushed with normal saline to remove any external blood. Animals were euthanized by receiving a lethal dose of intravenous potassium chloride.

Scintigraphic analysis

After graft explantation, radiolabeled platelets deposited on the graft were counted for one minute immediately by using a gamma well counter (1470 WIZARD; Wallac, Turku, Finland) for a quantitative analysis. The number of radiolabeled platelets was expressed as counts per minute (cpm). Scintigraphic images were taken visually by using a large field-of-view gamma camera (E-CAM; Toshiba, Tokyo, Japan) equipped with a parallel-hole collimator. Images were acquired for a minimum of 500000 counts per view and stored in a 64 × 64 matrix. For a semi-quantitative analysis, region of interest (ROI) analysis([11]) was performed by using the iSSPView image program (version

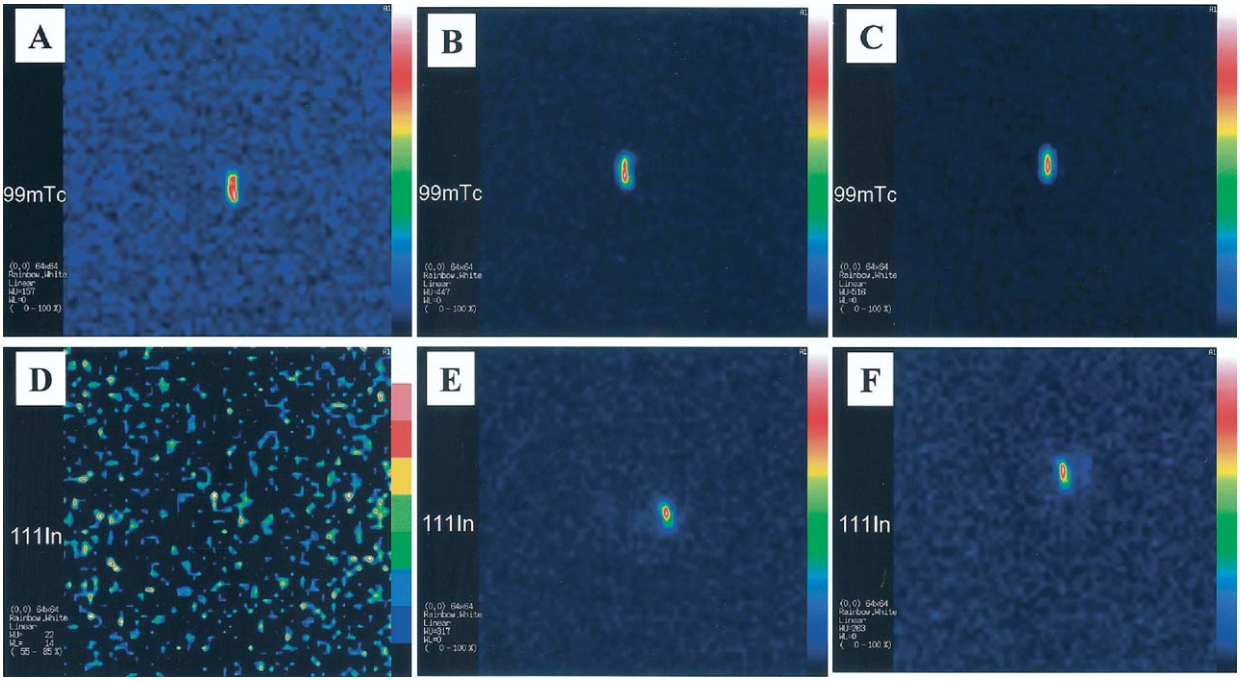

Fig 3. Scintigraphic images of the grafts in visual analysis. Top, Group I (^{99m}Tc-apcitide scintigraphy): (A) POD 1, (B) POD 7, (C) POD10. Bottom, Group II (^{111}In-platelet scintigraphy): (D) POD 1, (E) POD 7, (F) POD 10. Scintigraphic images in Group I were visualized earlier and more clearly than those in Group II. POD, postoperative day.

Table I. Detection rate for platelet deposition in scintigraphic images

Scintigraphy	*Positive(n)*	*Negative(n)*	*Detection rate(%)*
Group I (^{99m}Tc)	36	0	100*
Group II (^{111}In)	24	12	67

*P < 0.001 vs. Group II.

1.028, Nihon Medi-physics Co., Ltd., Hyogo, Japan). Briefly, graft ROI (10 × 5 pixels) was traced on the scintigraphic image of vascular prosthesis (Figure 1) and platelet activity of the graft ROI was measured and expressed as counts per pixel (cpp). Both visual and semi-quantitative analyses were performed by two experienced observers (Y.I. and H.K.) who were unaware of the data of quantitative analysis.

Statistical analysis

All values are expressed as the means ± standard deviation (SD). After scintigraphic image and data analysis, subsequent statistical analyses were performed with the Statview (Version 5.0) software package (Abacus Concepts Inc, Berkeley, CA). To evaluate the validity of ^{99m}Tc-apcitide scintigraphy in the assessment of platelet deposition, time-dependent curves of platelet deposition or graft ROI in both groups were compared by two-way analysis of variance (ANOVA). Scintigraphic images were classified "positive" or "negative", depending on whether or not it was possible to detect the platelet deposition visually. The differences between the two groups with regard to the detection rate for platelet deposition in scintigraphic images were analyzed using the McNemar χ^2 test. Simple linear regression analysis was performed by the least squares method to determine the relationship between platelet activity of graft ROI in semi-quantitative analysis and radiolabeled platelet deposition of graft in quantitative analysis in each group. The linear regression line was set to start at the origin (y intercept, zero) because of theoretical hypothesis. *P* value of less than 0.05 was considered statistically significant.

RESULTS

All grafts in both groups were patent without macroscopic stenosis and thrombus. Radiolabeled platelet deposition of the grafts in quantitative analyses, which was evaluated by using a gamma well counter, was shown in Figure 2. In Group I and II, the radiolabeled platelet deposition increased steeply after postoperative day (POD) 3 and reached a maximal level on POD 10. Afterward it decreased gradually. Although the two-way ANOVA revealed no significant difference in time-dependent changes of radiolabeled platelet deposition between the two groups (F=1.7, P=0.15), the radiolabeled platelet deposition in Group I was significantly higher that that in Group II on

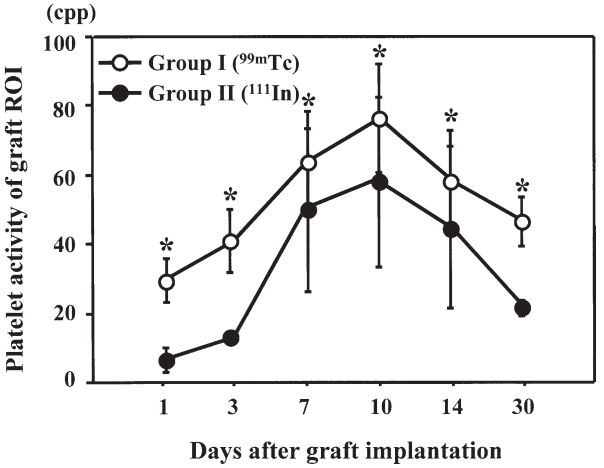

Fig 4. Platelet activity of graft ROI in semi-quantitative analysis. Although there was no statistically significant difference in time-dependent changes of platelet activity of graft ROI between both groups, the platelet activity in Group I was significantly higher than that in Group II on each day after graft implantation. *P<.01 vs. Group II. ROI, region of interest.

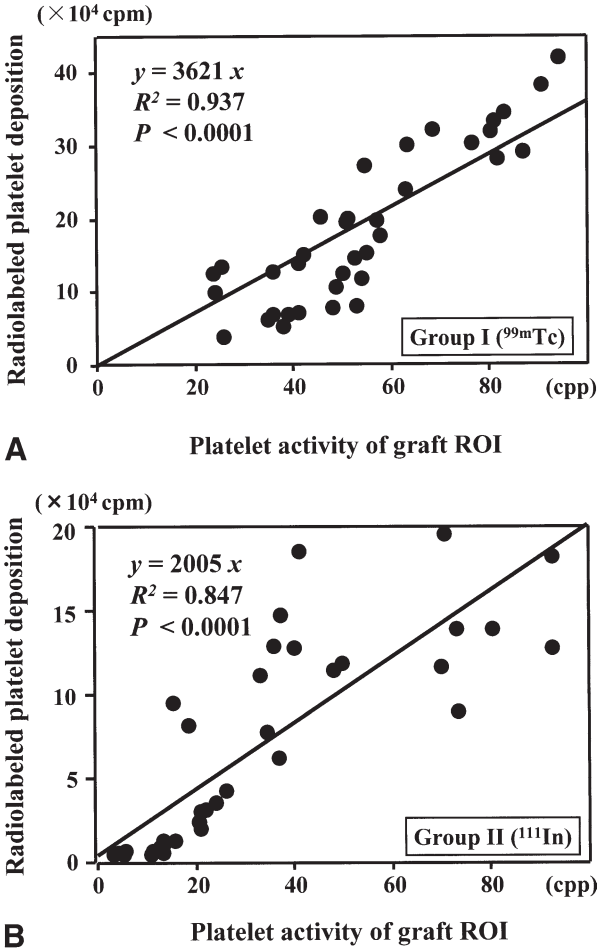

Fig 5. Correlation between platelet activity of graft ROI in semi-quantitative analysis and radiolabeled platelet deposition of graft in quantitative analysis. (A) Group I, (B) Group II. There was a significant correlation with high coefficient determination between the platelet activity and the radiolabeled platelet deposition in each group. ROI, region of interest.

each POD ($P<.0001$ on POD 1, 3, 10 and 30, $P=.0005$ on POD 7 and 14).

Visual analyses in both groups were shown in Figure 3. Scintigraphic images in Group I were visualized earlier and more clearly than those in Group II. In Group II, the images on POD 1 and 3 were so indistinct that it was difficult to trace them for graft ROIs (Figure 3-D). The detection rate for platelet deposition in the present study was 100% in Group I, whereas 67% in Group II (Table I). Scintigraphy in Group I showed a significantly greater detection rate than that in Group II with McNemar χ^2 test ($P<.001$). Semi-quantitative analyses of scintigraphic images were shown in Figure 4. Although the two-way ANOVA revealed no significant difference in time-dependent changes of platelet activity of graft ROI ($F=1.1$, $P=.39$), the platelet activity in Group I was significantly higher than that in Group II on each POD ($P<.0001$ on POD 1, 3 and 30, $P=.0025$ on POD7, $P=.0012$ on POD10, $P=.0038$ on POD14). In each group, the simple regression analysis revealed that platelet activity of graft ROI in semi-quantitative analyses correlated significantly with radiolabeled platelet deposition of graft in quantitative analysis ($P<.0001$, respectively), as shown in Figure 5.

DISCUSSION

[^{99m}TcO] apcitide, the technetium complex of the 13 amino acid, apcitide, *cyclo*-($_D$-Tyr-Apc-Gly-Asp-Cys)-Gly-Gly-Cys(Acm)-Gly-Cys(Acm)-Gly-Gly-Cys-NH_2, where Apc is $_L$-[*S*-(3-aminopropyl)]cystein (an arginine mimetic) and Acm is the acetamidomethyl protecting group, has high affinity and selectivity for the GPIIb/IIIa receptor that is expressed on the membrane surface of activated platelets and plays an integral role in platelet aggregation and thrombus formation. Bibapcitide, a 26 amino acid, bis-succinimidomethyl ether-linked dimmer of the peptide apcitide has been formulated as a single-vial, lyophilized kit having the trade name AcuTect. When sterile, nonpyrogenic sodium pertechnetate ($^{99m}TcO_4^-$) in 0.9% sodium chloride is added to AcuTect radiopharmaceutical kit and the resulting kit is heated, [^{99m}TcO] apcitide forms. This is the first radiopharmaceutical to target acute deep vein thrombosis (DVT) in the lower extremities([12]). Patient studies indicated that scintigraphy using [^{99m}TcO] apcitide is a safe and sensitive method for diagnosing acute DVT([8]). Scintigraphic techniques can be used to determine the location and extent of the active (acute) thrombi and ^{99m}Tc is the preferred radionuclide for diagnostic nuclear medicine because of its ideal physical properties (6.02 h half-life, 140keV, *r*-emission), high purity, commercial availability and low cost. Our primary concept in this study is to apply AcuTect to the assessment of platelet deposition in small caliber vascular prostheses.

Traditional methodology of the investigation of platelet deposition in the field of small caliber vascular prostheses is ^{111}In-platelet scintigraphy. There are many studies of acute thrombus, platelet deposition and antiplatelet medication with ^{111}In-platelet scintigraphy in clinical and experimental applications([1-3]). We also studied platelet deposition of fibrin-coated small caliber vascular prostheses that we used in the present study recently([5;13]). However, ^{111}In-platelet scintigraphy has several drawbacks as previously reported. First, the harvesting of autologous platelets must need various processes before injection in an activated state and the radiolabeling efficiency of harvested platelets is affected by the processing condition([14]). Secondly, the relatively long radiopharmaceutical half-life of ^{111}Indium (2.8 days) precludes serial observations([15]). Thirdly, ^{111}In-platelets have demonstrated slow blood clearance, resulting in poor target-to-background ratios over the course of several hours after injection([16]). The need to delay evaluation for 24 hours after injection of ^{111}In-platelets hinders rapid diagnosis of thrombosis([17]). In addition, our recent report ([5]) indicated some another limitations of ^{111}In-platelet scintigraphy including the limited sensitivity. ^{111}In-platelet scintigraphy has low sensitivity for the inactive (chronic) thrombus and small platelet deposition of less than 1.2×10^4 cpm to acquire a good-quality of scintigraphic image.

The present study demonstrated that ^{99m}Tc-apcitide can reliably evaluate platelet deposition in small caliber vascular prostheses in a rabbit model. The platelet deposition, which was not detected macroscopically, was quantified accurately by ^{99m}Tc-apcitide scintigraphy. Between ^{99m}Tc-apcitide scintigraphy and ^{111}In-platelet scintigraphy, there was no statistically significant difference in time-dependent changes of radiolabeled platelet deposition in quantitative analysis and platelet activity of graft ROI in semi-quantitative analysis on small caliber vascular prostheses. In both scintigraphies, the platelet activity of graft ROI was significantly correlated with the radiolabeled platelet deposition with high coefficient determination. However, ^{99m}Tc-apcitide scintigraphy was able to visualize platelet deposition earlier and more clearly than ^{111}In-platelet scintigraphy, and detection rate for platelet deposition in ^{99m}Tc-apcitide scintigraphy was significantly higher than that in ^{111}In-platelet scintigraphy. The radiolabeled platelet deposition and the platelet activity of graft ROI in ^{99m}Tc-apcitide scintigraphy was also significantly higher than those in ^{111}In-platelet scintigraphy. It was because positive scintigraphic images are associated with a high nuclear activity. ^{99m}Tc-apcitide scintigraphy has a higher nuclear activity (740MBq) in accordance with the standard protocol, compared with ^{111}In-platelet scintigraphy (10 to 37 MBq). Moreover, ^{99m}Tc-apcitide scintigraphy can identify all platelets both which are already deposited on the luminal surface of graft and which are newly attached during 2 hours after the injection of ^{99m}Tc-apcitide, by binding to these platelets. On the other hand, ^{111}In-platelet scintigraphy can only identify new platelets which are attached on the luminal surface of graft during 24 hours after the injection of ^{111}In-platelets, and it can detect only ^{111}In-platelet deposition in the new platelet deposition visually. This difference of the identification of platelet deposition between ^{99m}Tc-apcitide scintigraphy and ^{111}In-platelet scintigraphy can also explain the difference of their sensitivity in visual analysis.

The preparation of ^{99m}Tc-apcitide was simple and easy. It took approximately 30 minutes for the radiolabeled preparation in ^{99m}Tc-apcitide scintigraphy in this study, whereas 2 to 3 hours in ^{111}In-platelet scintigraphy. The major technical advantage in ^{99m}Tc-apcitide scintigraphy was no need for harvesting and radiolabeling autologous platelets. It gave great benefits of not only short preparation time but also no invasion for animals and stable radiolabeling efficiency. Moreover, ^{99m}Tc-apcitide scintigraphy can take an early imaging of platelet deposition (10 to 60 minutes postinjection), which enable to detect acute thrombosis immediately. The short radiopharmaceutical half-life of ^{99m}Technetium has a potential to make serial observations of platelet deposition. In addition to these advantages, ^{99m}Tc-apcitide scintigraphic imaging provides images of good quality with good sensitivity, which we showed in this study. The above-mentioned characteristics of ^{99m}Tc-apcitide scintigraphy are very useful to assess platelet deposition in small caliber vascular prostheses, especially in a clinical situation. It is important to check the graft status and the effect of antiplatelet medication after cardiovascular surgery. We can get significant information of the present platelet deposition on the implanted graft by using ^{99m}Tc-apcitide scintigraphic imaging, and can respond to the result quickly. The postoperatively accurate evaluation and quick response for platelet deposition may bring an improvement of graft patency. Although ^{111}In-platelet scintigraphy is not popularized clinically in the assessment of small caliber vascular prostheses in the field of cardiovascular surgery, we believe that ^{99m}Tc-apcitide scintigraphy will become a standard methodology for the assessment in the clinical setting.

The limitation of this study is that there were no thrombotic events as graft stenosis and occlusion. Betes et al. reported that ^{99m}Tc-apcitide scintigraphy can detect new, actively forming thrombi as abnormal results whereas old, inactive thrombi as normal results in the presence of residual abnormalities ([18]), as same as ^{111}In-platelet scintigraphy. Further studies of ^{99m}Tc-apcitide scintigraphy are still required to evaluate the pattern of platelet deposition in graft thrombosis.

In conclusion, ^{99m}Tc-apcitide scintigraphy is a new diagnostic examination to evaluate platelet deposition in small caliber vascular prostheses. This methodology has more advantages including simple preparation, noninvasive technique, early and accurate detection for platelet deposition and is superior to ^{111}In-platelet scintigraphy. ^{99m}Tc-apcitide scintigraphy has a potential utility in assessment of platelet deposition in the field of cardiovascular surgery and may be used as an alternative to ^{111}In-platelet scintigraphy in the detection of acute thrombosis.

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